

**REMARKS**

Claims 75, 77-112, and 113-133 are presently pending. Claims 75, 98, 99, and 104 have been amended to correct claim informalities. The amendment to the claims, as such, does not add new matter. The applicants respectfully request the examiner to consider the following remarks in light of the presently pending claims.

**I. 35. U.S.C. §112, Second Paragraph Rejections**

Reconsideration is respectfully requested of the rejection of claims 75, 77-104, and 113-133 under 35 U.S.C. § 112, second paragraph. The Office has rejected the claims as indefinite because of the recitation of the phrase “an acceptable diluent, adjuvant, or excipient.” Per the claim amendments, this phrase has been deleted. In view of the amendment, claims 75, 77-104, and 113-133 are definite, and the rejection is moot.

The Office has also rejected claim 104 as being indefinite for lack of antecedent basis in view of the phrase “said animal food.” Claim 104 has been amended to recite “the food.” Claim 75 from which claim 104 depends recites “food.” In accordance, with this amendment claim 104 has proper antecedent basis for “food” and the rejection is moot.

**II. 35. U.S.C. § 103 Rejections**

For the reasons detailed below, all pending claims are not rendered obvious by any single reference, or combination of references cited by the Office.

***(a) The claims are not rendered obvious by Ivey et al., Blake et al., and Bland et al.***

Reconsideration is requested of the rejection of claims 75, 77-80, 82-87, 90-93, 96-98, 104, 113, 115-119 and 133 under 35 U.S.C. 103 (a) in view of U.S. Patent No. 5,928,686 ('686 patent, i.e., Ivey et al) as evidenced by U.S. Patent No. 2,938,053 ('053 patent, i.e., Blake et al.) and in view of U.S. Patent No. 5,591,467 ('467 patent, i.e., Bland et al.).

Three criteria must be present to establish a *prima facie* case of obviousness.<sup>1</sup> First, the prior art reference must teach or suggest all the claim limitations. Second, there must be some suggestion or motivation in the knowledge generally available to one of ordinary skill in the art to modify the reference. Third, there must be a reasonable expectation of success.<sup>2</sup> Not one of these three criteria is satisfied by the combination of the '686 patent, the '053 patent, and the '467 patent.

Claim 75 is directed to a method of killing microbes in food or water. The method comprises treating the food or water with an antimicrobial composition. The antimicrobial composition comprises **at least two organic acids** selected from the group **consisting of** formic acid, butyric acid, fumaric acid, lactic acid, benzoic acid, and propionic acid; and a third organic acid that is a compound of formula (I).

(i) **no motivation to combine references**

The '686 patent discloses a feed ration that among other ingredients has Alimet<sup>®</sup> (i.e., 2-hydroxy-4-(methylthio)butanoic acid), propionic acid, and citric acid.<sup>3</sup> The '053 patent discloses that 2-hydroxy-4-(methylthio)butanoic acid is a beneficial amino acid analogue nutrient for use in animal feeds, and particularly in poultry feed.<sup>4</sup> Nowhere do either the '686 patent or the '053 patent disclose or suggest an antimicrobial composition **useful for killing microbes in feed or water** that comprises **at least two organic acids** selected from the group **consisting of** formic acid, butyric acid, fumaric acid, lactic acid, benzoic acid, and propionic acid; and a compound of formula (I), as required by claim 75.

Resort to the '467 patent does not cure the defect in the Office's obviousness case. The '467 patent teaches the **benefit of formaldehyde** as a feed additive for killing microbes and provides a spray method for applying

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<sup>1</sup> MPEP §2143.

<sup>2</sup> *Id.*

<sup>3</sup> '686 patent at column 7.

<sup>4</sup> '053 patent at column 1.

formaldehyde to the feed. Formaldehyde is not recited in the organic acid combination of claim 75. Moreover, formaldehyde is not even an organic acid. Rather it is an aldehyde. In fact, the '467 patent expressly teaches that organic acids such "as lactic acid, propionic acid, formic acid, butyric acid, sorbic acid, benzoic acid and combinations of these" are **generally ineffective** as bacteriocidal agents **in animal feed stuffs**.<sup>5</sup> Because of the ineffectiveness of organic acids, the '467 patent teaches the use of aldehydes to prevent microbe growth in animal feed. The '467 patent specifically recites:

...[i]t is now generally recognized that limiting the introduction of Salmonella through the feed is the most effective long range plan for improving the situation and many compounds with known bacteriocidal properties, such as lactic acid, propionic acid, formic acid, butyric acid, sorbic acid, benzoic **acid and combinations of these** have been tested. While many of these agents kill bacteria **in solution, they do not kill all bacteria in animal feed stuffs**.<sup>6</sup>

In view of this passage, a skilled artisan **would not be motivated** to combine the disclosure of the '467 patent with that of the '686 patent, and the '053 patent to arrive at the use of an organic acid combination recited by claim 75. The '467 patent, when properly viewed in its entirety, **teaches away** from the use of the listed organic acids **or their combinations** because they are said to be ineffective at killing bacteria in animal feed. Stated plainly, the whole point of the present invention as defined by claim 75 is antimicrobial organic acid combinations that kill microbes **in feed** or water. Moreover, the '467 patent teaches the benefits of using **aldehydes** in lieu of organic acids for killing microbes in feed because, as stated previously, organic acids are taught to be "ineffective" for this purpose. Taken together, a skilled artisan empowered with the cited art cannot fairly be deemed to be motivated to select formic acid and hydroxyl-methylthio butanoic acid (as disclosed by the '686 patent and '053 patent) and combine them with any of lactic acid, propionic acid, butyric acid, sorbic acid, benzoic acid (as disclosed by the '467 patent) to arrive at an organic

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<sup>5</sup> '467 patent, at column 2, lines 18 to 26 (emphasis added).

<sup>6</sup> '467 patent, at column 2, lines 18 to 26 (emphasis added).

acid combination recited in claim 75. This teaching away by the '467 patent undercuts any supposed motivation to combine, and supports a finding of non-obviousness.

**(ii) no reasonable expectation of success**

A skilled artisan also would not have a reasonable expectation of success for obtaining organic acid combinations that are effective for killing microbes in feed or water in view of the disclosure of the prior art. In fact, the '467 patent explicitly teaches of the difficulty encountered when attempting to kill microbes in animal feedstuffs with organic acids. Because of this difficulty, the '467 patent teaches the use of aldehydes to prevent microbe growth in animal feed in lieu of organic acids. The applicants' own data submitted with this response confirms that several of the organic acids recited in claim 75 (and described in the '467 patent as "ineffective") are generally ineffective at killing *Salmonella* in feed when used singly.<sup>7</sup> Considered collectively, the prior art has not shown that the individual elements are sufficient to meet the limitations of the claimed invention, and the previously submitted Declaration of Dr. Knight further shows that the individual organic acids are inadequate for the limitations of the claimed invention (i.e. "for food or water"). All of this supports an allowance of the presently pending claims.

Moreover, the general state of knowledge in the microbial arts supports the notion that the effective selection of organic acids for use as antimicrobial agents is unpredictable. The Warnecke et al. review article exemplifies this unpredictability.<sup>8</sup> Individual organic acids uniquely, and at times unpredictably, impact microbe cell growth, regulatory pathway, turgor pressure, and cell

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<sup>7</sup> See the 37 C.F.R. Declaration of Dr. Christopher Knight, at paragraph 4, which was submitted with the response to the Office Action dated March 27, 2007. In the Declaration, it is shown that HMTBA, butyric acid, and lactic acid, are generally ineffective at killing *Salmonella* in feed when used singly. Data showing that propionic acid alone is also generally ineffective at killing *Salmonella* in feed is submitted with this response.

<sup>8</sup> Warnecke, T., and Gill, R., *Microbial Cell Factories* (2005) 4:25, a copy of which was submitted with the response to the Office Action dated March 27, 2007.

landscape.<sup>9</sup> As such, every organic acid may potentially cause a unique response by an individual microorganism. As many microorganisms may live and thrive in acidic environments, it is not sufficient to infer that a single organic acid useful against one microbe will provide the same utility against a different microbe. Additionally, the degree of bioavailability (i.e., ability to reach the target microbe) varies for different organic acids, and different microbes are resistant to different pH ranges. With this degree of unpredictability, a skilled artisan empowered with the cited prior art and the general knowledge of the microbial arts would not have a reasonable expectation of success for obtaining organic acid combinations recited in claim 75 that are effective for killing microbes in feed or water.

Nowhere do any of the '686 patent, the '053 patent, and/or the '467 patent disclose or suggest an antimicrobial composition useful for killing microbes in feed or water that comprise **at least two organic acids** selected from the group **consisting of** formic acid, butyric acid, fumaric acid, lactic acid, benzoic acid, and propionic acid; and a compound of formula (I), as required by claim 75. Moreover, nowhere do any of the cited references disclose or suggest the benefit of this specific combination of organic acids to kill microbes in feed or water. In the absence of any disclosure of use of the specific combinations of organic acids to kill microbes in feed or water as recited in claim 75, a *prima facie* case

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<sup>9</sup>Id. For example, see the third page, column two of the article, which states: **Organic acid anions affect cell growth in a variety of manners.** Increased anion concentration has been shown to lead to an increased transport of potassium ions into the cell, which increases turgor pressure [47,48]. To maintain a constant turgor pressure and cell volume, glutamate is transported out of the cell [48]. This transport activity concomitantly disrupts the osmolarity of the cytoplasm, which in turn lowers the cell's growth potential and viability. In addition to this general anion effect, **there are also effects specific to each organic acid.** It has been proposed that enzymes involved in protein synthesis are sensitive to a combination of two unrelated mechanisms, including the acidification of pHi and the formation of an anionic pool [35]. Although this finding implies that the **organic inhibition due to the anion pool could be acid specific,** the details describing this dual inhibition mechanism remain unclear. Kirkpatrick et al. reported proteins exhibiting increased expression in response to extracellular acetate [33]. Among these are the OppA transporter, RpoS regulon, several amino acid uptake proteins, DNA binding proteins, and extreme-acid preplasmic chaperones. Interestingly, when formate was introduced in place of acetate the expression of the previously mentioned proteins was repressed, **indicating that the response was anion specific.** This finding introduces new challenges in addressing organic acid tolerance. Specifically, it highlights the need to engineer both pH and as well as specific anion tolerance into host organisms. (Emphasis added).

for obviousness is lacking. Moreover, claims 77-80, 82-87, 90-93, 96-98, 104, 113, 115-119 and 133 recite all of the elements of claim 75 and are likewise not obvious in view of the cited art for the reasons detailed above.

**(iii) indicia of non-obviousness**

Even assuming, *arguendo*, that a *prima facie* case of obviousness has been established in view of the cited art, this case can be rebutted by showing that the claimed organic acid antimicrobial combinations of claim 75 achieves unexpected results. The claimed combinations, in fact, do provide unexpected results. As stated by Dr. Christopher Knight in his Declaration:

... [w]e have research data, that in my opinion, demonstrates surprising and unexpected results for organic acid formulations falling within the scope of the '434 patent claims. As an example, attached to this Declaration is a graph (identified as figure 7) that depicts a synergistic effect for two organic acid formulations of the claimed invention. With reference to the attached graph, data is depicted for the antimicrobial activity of five different organic acid compositions against *Salmonella* in feed. The five organic acid compositions include: (1) 0.45% HMTBA alone (i.e., 2-hydroxy-4-(methylthio)butanoic acid, which is a compound of Formula (I) in the '434 application); (2) 0.45% butyric acid alone; (3) 0.45% lactic acid alone; (4) blend OA 4, which is 0.15% lactic acid, 0.15% propionic acid, and 0.15% HMTBA; and (5) blend OA 6, which is 0.1% lactic acid, 0.1% butyric acid, 0.1% propionic acid, and 0.15% HMTBA. The antimicrobial experiments were conducted in accordance with Novus's standard protocol entitled "low pH in Feed Test Procedure," a copy of which is attached to this Declaration. As depicted in the graph, the antimicrobial activity of either blend OA 4 or blend OA 6 achieved significantly higher killing of *Salmonella* at lower concentrations than could be achieved with any of the single organic acids alone.<sup>10</sup>

While synergism is not a requirement of non obviousness<sup>11</sup>, it has been shown that synergism exists in the present case. The combination of the claimed invention is substantially greater than the additive effect of what would be

<sup>10</sup> 37 C.F.R 1.132 Declaration of Dr. Christopher Knight, at paragraph 4, a copy of which was submitted with the response to the Office Action dated March 27, 2007.

<sup>11</sup> *Gardner v. TEC Sys. Inc.*, 725 F.2d 1338, 1349 (Fed. Cir. 1984) (in banc).

expected from the individual components. Stated another way, if the data depicted in Figure 7 aren't expressed in cfu, but rather in actual number of colonies killed, the result is even more striking. Blend OA 4 and Blend OA 6 have approximately a 10-fold improvement compared to any of the single organic acid compositions tested. When synergism is present, particularly in a chemical case, it is indicative of non-obviousness.<sup>12</sup> As such, the demonstrated synergistic effect of the organic acid combinations for killing microbes in food or water is yet additional evidence that supports a finding of non-obviousness and supports allowance of all pending claims.

In the present Office action, the Office states that the results submitted via Dr. Knight's Declaration are "not convincing" because no data is shown for propionic acid alone. In response, applicants have submitted a graph that illustrates the ineffectiveness of propionic acid alone in the *Salmonella* feed test (i.e., the same test reported in Dr. Knight's Declaration). Propionic acid was tested for its ability to kill *Salmonella* in feed at concentrations of 0%, 0.25%, 0.5%, 0.75%, and 1.0%. As depicted in the graph, propionic acid is not effective at killing *Salmonella* at any of the tested concentrations. Blend OA 4 and OA6 contain 0.15% and 0.1% propionic acid, respectfully. Clearly, the synergistic effect exhibited by OA4 and OA6 is not due to propionic acid alone.

The Office has also stated that the results depicted in figure 7 are not commensurate with the scope of the claims because only one microbe is killed (i.e., *Salmonella*) and only two iterations of organic acid combinations are tested (i.e., OA4 and OA6). It would be virtually impossible to test every possible combination of organic acids at every possible range against every possible microbe. The applicant has tested exemplary organic acid combinations against a major parasite that grows on/in animal feed— *Salmonella*. Moreover, claims 127 and 128 specifically recite that the organic acid combination is OA6, new claim 134 depends from claim 127 and requires the microbe to be *Salmonella*. New claim 135 specifically recites that the organic acid combination is OA4, and

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<sup>12</sup> *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1540 (Fed. Cir. 1983).

new claim 136 requires the microbe to be *Salmonella*. In view of this, minimally, claims 127, 128, 134, 135, and 136 are commensurate with the demonstrated unexpected result.

**(iv) response to the Office's obviousness case**

According to the Office, however, it would have been obvious to combine three separate compositions (i.e., 2-hydroxy-4-(methylthio)butanoic acid as disclosed in the '686 patent and '053 patent, with two of lactic acid, propionic acid, and butyric acid (as disclosed in the '467 patent) to form a third composition that is used for the very same purpose (i.e., as an organic acid to kill microbes in feed). In essence, the Office erroneously appears to view the present invention as nothing more than green plus green equals greener. But the cited art, taken together or singly, provides no basis for this conclusion. In fact, the two lynchpins of the Office's obviousness argument—that the individual organic are effective at killing microbes in feed or water—is flawed.

In the first instance, in contrast to the Office's assertion, neither the '686 patent nor the '053 patent establish that 2-hydroxy-4-(methylthio)butanoic acid is effective at killing microbes **in feed or water**, as required by claim 75. The Office acknowledges this point with respect to the '686 patent, but cites the '053 patent to make this showing. In particular, the Office states "as evidenced by Blake et al. 2-hydroxy-4-(methylthio)butanoic acid has antimicrobial activity, antifungal activity, and is used in animal diet particularly poultry. See column 1, lines 39-41, lines 47-50, [and] lines 58-63."<sup>13</sup> This statement is not correct. Not one of the passages of column 1 cited by the Office establishes that 2-hydroxy-4-(methylthio)butanoic acid is effective in killing microbes **in feed or water**. The third paragraph of column 1 in which lines 39-41 appears specifically recites:

...[o]ther **methionine** analogues differ considerably from the natural methionine in molecular structure and because of the unnatural configuration are not useful as animal or plant feed

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<sup>13</sup> Office Action dated December 11, 2007 at page 5.



supplements. Many of these are absorbed by plant and animal structures and have toxic effects due to the inability of the organism to assimilate the analogue. By proper regulation of rates of application the toxic effect may be limited to parasitic life without being deleterious to the plant or animal host. Thus many of **the new compounds** are useful as fungicides, bactericides, virus control agents, anethelminthics, and nematocides, through antimetabolic action.<sup>14</sup>

The “new compound” referred to in the last sentence of this passage as having antimicrobial activity is not 2-hydroxy-4-(methylthio)butanoic acid. To glean this from column 1, however, the second and third paragraphs must be read in their entirety. The second paragraph discusses the methionine analogues of the invention, which includes methionine 2-hydroxy-4-(methylthio)butanoic acid. The third paragraph, as shown above, starts with the phrase “**other** methionine analogues” to contrast the methionine analogues of paragraph two (i.e., the methionine analogues of the invention) with prior art methionine analogues. The rest of paragraph three, including the last sentence, discloses features of prior art methionine analogues. In this context, the antimicrobial/antiparasitic properties referenced in the last sentence of paragraph 3 refers to prior art methionine analogs and not methionine 2-hydroxy-4-(methylthio)butanoic acid. Importantly, while this last sentence refers to antimicrobial/antiparasitic properties of prior art methionine analogues, nowhere does this sentence disclose or suggest that the methionine analogues are effective at killing microbes in feed or water, as required by claim 75.

Equally, lines 47-50, and lines 58-63 of column 1 cited by the Office fail to establish that 2-hydroxy-4-(methylthio)butanoic acid is effective in killing microbes **in feed or water**. In particular, lines 47-50 state that a purpose of the invention described in the ‘053 patent is to provide “a means for preparing inexpensive animal diets and particularly poultry feed.” This passage does not disclose or suggest that 2-hydroxy-4-(methylthio)butanoic acid is effective at killing microbes **in feed or water**. Lines 58-63 state that another purpose of the

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<sup>14</sup> U.S. Patent No. 2,938,053, third paragraph, column 1 (emphasis added).

invention is to provide “new compounds” and methods “for elimination or control of plant or animal parasites.” This passage does not disclose or suggest that 2-hydroxy-4-(methylthio)butanoic acid is effective in killing microbes specifically located **in feed or water**. Moreover, the ‘053 patent discloses a process for making a genus of amide and acid compounds of which 2-hydroxy-4-(methylthio)butanoic acid is but a single species. Thus the “new compounds” referenced in lines 58-63 are not necessarily 2-hydroxy-4-(methylthio)butanoic acid. But for column 1, the ‘053 patent is silent regarding the antimicrobial activity of any compound.

In the second instance, the Office has not established that any of the organic acids listed in the ‘467 patent are effective at killing microbes in feed or water, as required by claim 75. Never-the-less, the Office uses the ‘467 patent in its obviousness case for the proposition that the reference teaches “animal feed compositions” that comprise the “antibacterial agents formic acid, propionic acid, and lactic acid.”<sup>15</sup> In this context, however, the Office has selectively cherry-picked the aforementioned sentence from the breadth of teaching provided by the ‘467 patent. This is not proper. Prior art references must be considered in their entirety. By this token, “[I]t is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.”<sup>16</sup> While the background of invention section of the ‘467 patent, as shown above, does state that formic acid, propionic acid, and lactic acid have bacteriocidal properties **in solution**, the next sentence goes on to state that these organic acids are **generally ineffective** as bacteriocidal agents **in animal feed stuffs**. As such, this passage does not disclose that any of these organic acids are effective at killing microbes in feed or water. Rather, the ‘467 patent teaches the opposite in that the recited organic acids are generally ineffective for this purpose. This is confirmed by the applicants’ own data submitted with this response that shows

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<sup>15</sup> See office action dated December 11, 2007 at page 5.

<sup>16</sup> *In re Wesslau*, 353 F.2d 238, 241, 147 U.S.P.Q. 391, 393 (C.C.P.A. 1965).

several of the organic acids recited in claim 75 (and described in the '467 patent as "ineffective") are generally ineffective at killing *Salmonella* in feed when used singly.<sup>17</sup>

Simply put, the Office has failed to demonstrate that the cited prior art teaches 2-hydroxy-4-(methylthio)butanoic acid, or any of the organic acids listed in the '467 patent are effective at killing microbes in feed or water. Without this showing, the Office has not established that the invention defined by claim 75 is obvious.

In support of its obviousness position, the Office cites *In re Kerkhoven*.<sup>18</sup> *Kerkhoven*, however, is distinguishable from the presently claimed invention. In *Kerkhoven*, the issue was whether the claimed process for the production of particulate detergent compositions containing a mixture of anionic and nonionic active detergent materials was patentable. The CCPA held that it was not, and, in so deciding stated "[i]t is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose."<sup>19</sup>

As an initial matter, the '686 patent, '053 patent, and the '467 patent fail to establish that the individual organic acids comprising the organic acid combination recited in claim 75 are effective at killing microbes in food or water. Importantly, *In re Kerkhoven* cannot properly be applied unless the individual organic acids forming the combination have known effectiveness at killing microbes in food or water. Absent some objective proof or showing, one of ordinary skill in the art cannot assume that any of the individual organic acids recited in claim 75 would necessarily be effective for the recited purpose (i.e., killing microbes in food or water). In fact, the evidence of record is to the

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<sup>17</sup> See the 37 C.F.R. Declaration of Dr. Christopher Knight, at paragraph 4, which was submitted with the response to the Office Action dated March 27, 2007. In the Declaration, it is shown that HMTBA, butyric acid, and lactic acid, are generally ineffective at killing *Salmonella* in feed when used singly. Data showing that propionic acid alone is also generally ineffective at killing *Salmonella* in feed is submitted with this response.

<sup>18</sup> *In re Kerkhoven*, 626 F.2d 848, 205 USPQ 1069 (CCPA 1980).

<sup>19</sup> *Id.* 626 F.2d. at 850, 205 USPQ at 1072.

contrary. Both the '467 patent and the applicants' own data<sup>20</sup> demonstrate that several of the recited organic acids in claim 75 are "ineffective" at killing microbes in feed or water when used singly.

Further, the instant situation involving claim 75 and the disclosure of the '686, '053, and '467 patents is distinguishable from the facts of *Kerkhoven*. In *Kerkhoven*, there was no reason to expect that the combination of detergent compositions could act differently from the individual compositions comprising it. In essence, *Kerkhoven* stands for the proposition that green plus green equals greener. While green plus green may equal greener in the detergent arts, as has been shown above, **the same cannot be said about the antimicrobial arts**. Moreover, one of skill in the art would not be able to use common sense to identify which organic acid combinations would be successful because each organic acid may provide subtle and different effects to the cell. In addition, the number of organic acid combinations that may reduce microbe viability is no small number, thus the proper combination cannot be easily tested or determined. The antimicrobial combinations of the present invention, per the claim elements, have an intended physiological effect—they must be able to kill a variety of living microbes in food or water. Thus, the ordinary and straightforward problem encountered by *Kerkhoven* of using a detergent to treat a stain cannot be properly applied to the assortment of considerations necessary for inhibiting or killing a diverse spectrum of living organisms in food or water, as required by the invention defined by claim 75.

In contrast to *Kerkhoven*, the facts of *Knoll Pharmaceutical*<sup>21</sup> are more analogous to the present invention defined by claim 75. In *Knoll Pharmaceutical*, the Federal Circuit disagreed with the district court that one of ordinary skill in the art would have had a reasonable expectation of

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<sup>20</sup> 37 C.F.R. 1.132 Declaration of Dr. Christopher Knight, at paragraph 4, a copy of which was submitted with the response to the Office Action dated March 27, 2007.

<sup>21</sup> *Knoll Pharmaceutical Co., Inc. v. Teva Pharmaceutical USA, Inc.*, 367 F.3d 1381, 70 U.S.P.Q.2d 1957 (Fed. Cir. 2004).

success of obtaining the claimed invention. Knoll's claims related to a combination of hydrocodone and ibuprofen. In support of holding the claims obvious, the district court found that the prior art expressly taught one of ordinary skill in the art to combine an opioid with an NSAID and that such a person would have a reasonable expectation for success of obtaining a composition useful for pain management because use of each agent (i.e., opioid and NSAIDS) is individually known in the prior art for pain management.<sup>22</sup> The Federal Circuit, however, found "no record of evidence of prior art teaching or suggesting the enhanced biomedical effect of the combination of hydrocodone and ibuprofen" as demonstrated in the invention.<sup>23</sup>

Similar to *Knoll Pharmaceutical*, a skilled artisan would not have a reasonable expectation of success for obtaining organic acid combinations that are effective for killing microbes in feed or water in view of the prior arts' disclosure. Lack of a reasonable expectation of success is even more apparent in the present case compared to *Knoll Pharmaceutical*, because unlike *Knoll Pharmaceutical*, the prior art cited in the present case does not demonstrate that the individual organic acids forming the organic acid combination are effective at killing microbes. Notably, the '467 patent expressly teaches that individual organic acids recited in claim 75 and their combinations are **generally ineffective** as bacteriocidal agents **in animal feed stuffs**.<sup>24</sup>

The Office has not set-forth any sufficient art-based rationale as to why a person of skill in the art would have been motivated to modify the organic acid composition as taught by the '686 patent and the '053 patent (i.e., hydroxyl-methylthio butanoic acid), and combine it with the organic acid compositions as taught by the '467 patent (i.e., lactic acid, propionic acid, formic acid, butyric acid, sorbic acid, and benzoic acid), or combine both with other organic acids

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<sup>22</sup> *Id.*, 1384, 70 U.S.P.Q.2d at 1959-60.

<sup>23</sup> *Id.*, 70 U.S.P.Q. at 1960.

<sup>24</sup> '467 patent, at column 2, lines 18 to 26 (emphasis added).

generally known in the art to arrive at the organic acid combination recited in claim 75 that are effective in killing microbes in food or water. The mere identification in the prior art of each component of a composition **does not** show that the combination as a whole is obvious.<sup>25</sup> Rather, to establish a *prima facie* case of obviousness based on a combination of elements in the prior art, the law requires a motivation to select the references and **to combine them in the particular claimed manner to reach the claimed invention**.<sup>26</sup> Without this demonstration of the requisite motivation to make the Office's proposed modification, a *prima facie* case of obvious has not been established. Moreover, the Office has not established that a skilled artisan would have a reasonable expectation of success if its proposed modification were made.

In view of the foregoing, the Applicants respectfully request withdrawal of the obviousness rejection of claim 75. Claims 77-80, 82-87, 90-93, 96-98, 104, 113, 115-119 and 133 recite all of the elements of claim 75 and are likewise not obvious in view of the cited art for the reasons detailed above with respect to claim 75.

***(b) The claims are not rendered obvious by Ivey et al., Blake et al., Bland et al., and Pinski et al.***

Reconsideration is requested of the rejection of claims 88-89 under 35 U.S.C. 103 (a) in view of U.S. Patent No. 5,928,686 ('686 patent, i.e., Ivey et al) as evidenced by U.S. Patent No. 2,938,053 ('053 patent, i.e., Blake et al.) in view of U.S. Patent No. 5,591,467 ('467 patent, i.e., Bland et al.) and US Patent Publication No. 2003/0172737 ('737 application, i.e., Pinski et al.).

Claim 88 is directed to a method of killing microbes in food or water that is fed to an aquaculture animal. The method comprises treating the food or water with an antimicrobial composition. The antimicrobial composition comprises **at least two organic acids** selected from the group **consisting of** formic acid,

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<sup>25</sup> *In re Kahn*, 441 F.3d 977, 986 (Fed. Cir. 2006) (citing *In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998)).

<sup>26</sup> *Id.*

butyric acid, fumaric acid, lactic acid, benzoic acid, and propionic acid; and a third organic acid that is a compound of formula (I).

The '686 patent, '053 patent, and the '467 patent are discussed above in II(a). Resort to the '737 application does not cure the defect in the Office's obviousness rejection as articulated in section II(a). The '737 application discloses use of a "liquid antimicrobial" to stabilize "encapsulated, oil-coated, moisturized feed against spoilage."<sup>27</sup> According to the '737 application, the liquid antimicrobial may be selected from the following group:

...a calcium salt of propionic acid, a sodium salt of propionic acid, an ammonium salt of propionic acid, acetic acid, a calcium salt of acetic acid, a sodium salt of acetic acid, citric acid, a calcium salt of citric acid, a sodium salt of citric acid, phosphoric acid, sorbic acid sodium benzoate, potassium benzoate, calcium benzoate, sorbic acid, potassium sorbate, sodium benzoate and mixtures thereof.

Nowhere does the '737 application disclose that any of the above referenced "liquid antimicrobials" are effective at killing microbes in food or water that isn't "encapsulated", as required by claim 88. Moreover, of the rather long list of antimicrobials, only two (i.e., benzoate and propionic) are even recited in claim 88. Importantly, the '467 patent expressly teaches that these two organic acid (i.e., benzoate and propionic) **are not effective at killing microbes in animal feed stuffs**. This teaching away by the '467 patent undercuts any supposed motivation to combine the references cited in this rejection, and supports a finding of non-obviousness. This is particularly true in light of the fact that the antimicrobials are being used in the '737 patent for a different purpose compared to the purpose recited in claim 88 (i.e., to stabilize encapsulated food).

The Office has not set-forth any sufficient art-based rationale as to why a person of skill in the art would have been motivated to modify the organic acid composition as taught by the '686 patent and the '053 patent (i.e., hydroxyl-methylthio butanoic acid), and combine it with the organic acid compositions as

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<sup>27</sup> '737 application at paragraph [0010].

taught by the '467 patent (i.e., lactic acid, propionic acid, formic acid, butyric acid, sorbic acid, and benzoic acid), and combine them with the recited "liquid antimicrobials" disclosed in the '737 application or combine both with other organic acids generally known in the art to arrive at the organic acid combination recited in claim 88 that are effective in killing microbes in food or water. Moreover, the Office has not established that a skilled artisan would have a reasonable expectation of success if its proposed modification were made.

In view of the foregoing, the Applicants respectfully request withdrawal of the obviousness rejection of claim 88 and 89.

***(c) The claims are not rendered obvious by Ivey et al., Blake et al., Bland et al., and Friedman et al.***

Reconsideration is requested of the rejection of claims 94 and 95 under 35 U.S.C. 103 (a) in view of U.S. Patent No. 5,928,686 ('686 patent, i.e., Ivey et al) as evidenced by U.S. Patent No. 2,938,053 ('053 patent, i.e., Blake et al.) in view of U.S. Patent No. 5,591,467 ('467 patent, i.e., Bland et al.) and US Patent Patent 4,495,208 ('208 patent, i.e., Friedman et al.).

Claim 94 is directed to a method of killing microbes in food or water that is fed to a companion animal. The method comprises treating the food or water with an antimicrobial composition. The antimicrobial composition comprises **at least two organic acids** selected from the group **consisting of** formic acid, butyric acid, fumaric acid, lactic acid, benzoic acid, and propionic acid; and a third organic acid that is a compound of formula (I).

The '686 patent, '053 patent, and the '467 patent are discussed above in II(a). Resort to the '208 application does not cure the defect in the Office's obviousness rejection as articulated in section II(a). The '208 patent discloses a pet food formulation that contain may contain an organic acid. According to the '208 patent, the organic acid may be selected from the following group:



...citric, tartaric, gluconic, fumaric, glutaric, lactic, succinic, adipic, propionic, butyric, pentanoic, hexanoic, heptanoic, octanoic, nonanoic, decanoic, undecanoic, dodecanoic, lauric, and combinations of any of these with others of these or still other edible acids.<sup>28</sup>

Even more revealing, the '208 patent discloses that the "more preferred acids" are those selected from the group consisting of heptanoic, octanoic, and nonanoic.<sup>29</sup> None of the preferred organic acids are even recited in claim 94. The '208 patent provides no teaching or suggestion as to why a skilled artisan would be motivated to select one any of the recited organic acids and combine them with a compound having formula (I), as required by claim 94. If anything based on the teaching of the '208 patent, a skilled artisan would be directed to select heptanoic, octanoic, and nonanoic because they are disclosed as being "preferred." If the preferred organic acids were combined with a compound having formula (I), a skilled artisan would not arrive at the organic acid combination defined by claim 94.

Equally, a skilled artisan would not be motivated to select any of the organic acids recited in the '208 patent that are recited in claim 94 because the '467 patent expressly teaches that these organic acids are ineffective for killing microbes in animal feed stuffs. In particular, the '467 patent expressly teaches that lactic acid propionic acid butyric acid are **generally ineffective** as bactericidal agents **in animal feed stuffs**.<sup>30</sup> This teaching away by the '467 patent undercuts any supposed motivation to combine the references cited in this rejection, and supports a finding of non-obviousness.

The Office has not set-forth any sufficient art-based rationale as to why a person of skill in the art would have been motivated to modify the organic acid composition as taught by the '686 patent and the '053 patent (i.e., hydroxyl-methylthio butanoic acid), and combine it with the organic acid compositions as

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<sup>28</sup> '208 patent, column 3 last paragraph through column 4 first paragraph.

<sup>29</sup> *Id.*, column 4, lines 4 to 6.

<sup>30</sup> '467 patent, at column 2, lines 18 to 26 (emphasis added).

taught by the '467 patent (i.e., lactic acid, propionic acid, formic acid, butyric acid, sorbic acid, and benzoic acid), and combine them with the recited "pet food formulations" disclosed in the '208 application or combine both with other organic acids generally known in the art to arrive at the organic acid combination recited in claim 94 that are effective in killing microbes in food or water. Moreover, the Office has not established that a skilled artisan would have a reasonable expectation of success if its proposed modification were made.

In view of the foregoing, the Applicants respectfully request withdrawal of the obviousness rejection of claim 94 and 95.

***(d) The claims are not rendered obvious by Ivey et al., Blake et al., Bland et al., and Rolow et al.***

Reconsideration is requested of the rejection of claims 114, and 120-132 under 35 U.S.C. 103 (a) in view of U.S. Patent No. 5,928,686 ('686 patent, i.e., Ivey et al) as evidenced by U.S. Patent No. 2,938,053 ('053 patent, i.e., Blake et al.) in view of U.S. Patent No. 5,591,467 ('467 patent, i.e., Bland et al.) and US Patent 6,355,289 ('289 patent, i.e., Rolow et al.).

Claim 114 is directed to a method of killing microbes in food or water. The method comprises treating the food or water with an antimicrobial composition. The antimicrobial composition comprises **at least two organic acids** selected from the group **consisting of** formic acid, butyric acid, fumaric acid, lactic acid, benzoic acid, and propionic acid; and a third organic acid that 2-hydroxy-4-(methylthio)butanoic acid. Claim 114 further requires one of several recited acidulants.

The '686 patent, '053 patent, and the '467 patent are discussed above in II(a). Resort to the '289 application does not cure the defect in the Office's obviousness rejection. The '289 patent discloses a liquid preservation composition to extend the shelf life of tortillas made from corn. In a preferred embodiment, the preservation composition is said to comprise "phosphoric acid, propionic acid, and benzoic acid."

Notably, as stated above, the '467 patent expressly teaches that several of the individual organic acids recited in claim 114 and their combinations are **generally ineffective** as bacteriocidal agents **in animal feed stuffs**.<sup>31</sup> In particular, the '467 patent teaches that **two of the three** "preferred" preservatives disclosed in the '289 application, propionic acid and benzoic acid, **are not effective at killing microbes in animal feed stuffs**. This teaching away by the '467 patent undercuts any supposed motivation to combine the references cited in this rejection, and supports a finding of non-obviousness.

The Office has not set-forth any sufficient art-based rationale as to why a person of skill in the art would have been motivated to modify the organic acid composition as taught by the '686 patent and the '053 patent (i.e., hydroxyl-methylthio butanoic acid), and combine it with the organic acid compositions as taught by the '467 patent (i.e., lactic acid, propionic acid, formic acid, butyric acid, sorbic acid, and benzoic acid), and combine them with the recited tortillas shell preservatives disclosed in the '289 patent or combine both with other organic acids generally known in the art to arrive at the organic acid combination recited in claim 114 that are effective in killing microbes in food or water. Moreover, the Office has not established that a skilled artisan would have a reasonable expectation of success if its proposed modification were made.

In view of the foregoing, the Applicants respectfully request withdrawal of the obviousness rejection of claims 114, and 120 to 132.

**(e) The claims are not rendered obvious by Bland et al., and Paquet et al.**

Reconsideration is requested of the rejection of claims 75-82, and 96 under 35 U.S.C. 103 (a) in view of U.S. Patent No. 5,591,467 ('467 patent, i.e., Bland et al.) and Paquet (CA 1261855).

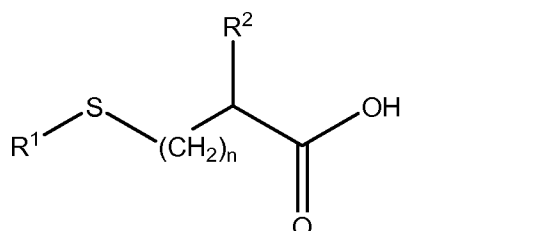
The elements of claim 75 are discussed in II(a).

The '467 patent is discussed above in II(a).

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<sup>31</sup> '467 patent, at column 2, lines 18 to 26 (emphasis added).

Resort to Paquet et al. does not cure the defect in the Office's obviousness rejection. Paquet et al. is asserted by the Office to disclose a compound that is said to read on Formula I of claim 75. This is not correct. Claim 75 recites a compound of formula (I) with the following structure:



wherein

R<sup>1</sup> is an alkyl group having from one to four carbon atoms;

n is an integer from 0 to 2;

R<sup>2</sup> is selected from the group consisting of hydroxy, amino, --OCOR<sup>3</sup>, or --NHCOR<sup>3</sup>; and

R<sup>3</sup> is an organic acid derivative.

Paquet et al. discloses an N-acyl-amino acid derivative having the following formula:

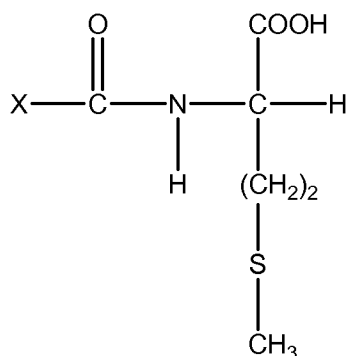


wherein:

X when taken in conjunction with CO is an acyl moiety; and

Y when taken in conjunction with NH is a D-amino acid or glycine moiety.

The only compound specifically disclosed by Paquet et al. that contains a sulfur group is when Y is methionine. In that iteration, the compound has the following structure:



As illustrated by this rough alignment between the substituents disclosed by Paquet et al (when Y comprises methionine or any other amino acid) and those required by claim 75, the particular combinations of substituents recited in Formula I is not disclosed by Paquet et al. The compounds of Formula I require a sulfur atom at one end of the molecule and a carboxylic acid at the other terminal of the molecule. While Paquet et al. disclose sulfur when Y is methionine, Paquet et al., **does not** comprise a carboxylic acid at the other end of the molecule irrespective of what moiety is selected for X. X is required to be an “acyl group.” By definition an acyl group is “an organic acid group in which the OH of the carboxylic group is replaced by some other substituent (RCO—). Examples: acetyl, CH<sub>3</sub>CO—; benzoyl, C<sub>6</sub>H<sub>5</sub>CO—. ”<sup>32</sup> Consistent with this definition, X does not include a carboxylic acid. Paquet et al. therefore does not disclose a group corresponding to the R<sub>2</sub>CCOOH moiety required by claim 75.

Accordingly, Paquet et al. does not disclose a compound of Formula I. In addition, Paquet et al. fails to suggest or teach any combination of organic acids for use in the preservation of food and water. Importantly, the recitation of a general N-acylamino acid formula does not teach or suggest any combination of distinct organic acids.

Even if the disclosures of Paquet et al. and the '467 patent are combined a skilled artisan would not arrive at the invention defined by claim 75. Simply put, neither reference discloses a compound having Formula 1, and neither reference

<sup>32</sup> Hawley's Condensed Chemical Dictionary, Thirteenth Edition, page 21, a copy of which is attached hereto.

discloses that compounds having Formula I are effective at killing microbes in food or water, as required by claim 75.

A skilled artisan also would not be motivated to combine the disclosure of Paquet et al. with the '467 patent. Notably, as stated above, the '467 patent expressly teaches that several of the individual organic acids recited in claim 75 and their combinations are **generally ineffective** as bacteriocidal agents in **animal feed stuffs**.<sup>33</sup> This teaching away by the '467 patent undercuts any supposed motivation to combine the references cited in this rejection, and supports a finding of non-obviousness.

Because Paquet et al. and the '467 patent do not disclose the claimed antimicrobial composition or provide any motivation for one skilled in the art to modify that which is disclosed to the antimicrobial composition of Claim 75, Applicants respectfully submit that claim 75 is patentable over the cited art. Each of claims 77-82, and 96 require the antimicrobial composition of claim 75, and therefore, are each likewise patentable over Paquet et al.

In view of the foregoing, the Applicants respectfully request withdrawal of the obviousness rejection of claims 75-82, and 96.

**(f) The claims are not rendered obvious by Rolow et al., and Doerr et al.**

Reconsideration is requested of the rejection of claims 75, 77, 97, 99-103, 113-117, and 133 under 35 U.S.C. 103 (a) in view of Doerr et al. (Poultry Science, 74(1), 23,1995), and US Patent 6,355,289 ('289 patent, i.e., Rolow et al.).

The elements of claim 75 are discussed in II(a).

Doerr et al. disclose that 2-hydroxy-4-(methylthio)butanoic acid may reduce mold growth in corn. But nowhere does this reference disclose the combination of 2-hydroxy-4-(methylthio)butanoic acid with other organic acids

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<sup>33</sup> '467 patent, at column 2, lines 18 to 26 (emphasis added).

recited in claim 75. Importantly, nowhere do Doerr et al. disclose or suggest the benefit of this combination for killing microbes in feed or water, as required by claim 75.

Resort to the '289 application does not cure the defect in the Office's obviousness rejection. The '289 patent discloses a liquid preservation composition to extend the shelf life of tortillas made from corn. In a preferred embodiment, the preservation composition is said to comprise "phosphoric acid, propionic acid, and benzoic acid." Nowhere does the '289 patent disclose or suggest combining a compound of Formula I with any of phosphoric acid, propionic acid, or benzoic acid, as required by claim 75.

A skilled artisan would not be motivated to combine the disclosures of Doerr et al. with the '289 patent to arrive at the invention defined by claim 75. Notably, as stated above, the '467 patent expressly teaches that several of the individual organic acids recited in claim 75 and their combinations are **generally ineffective** as bacteriocidal agents **in animal feed stuffs**.<sup>34</sup> In particular, the '467 patent teaches that **two of the three** "preferred" preservatives disclosed in the '289 application, propionic acid and benzoic acid, **are not effective at killing microbes in animal feed stuffs**. This teaching away by the '467 patent undercuts any supposed motivation to combine the references cited in this rejection, and supports a finding of non-obviousness.

The Office has not set-forth any sufficient art-based rationale as to why a person of skill in the art would have been motivated to modify combine 2-hydroxy-4-(methylthio)butanoic acid as disclosed by Doerr et al., and combine it with the recited tortillas shell preservatives disclosed in the '289 patent or combine both with other organic acids generally known in the art to arrive at the organic acid combination recited in claim 75 that are effective in killing microbes in food or water. Moreover, the Office has not established that a skilled artisan would have a reasonable expectation of success if its proposed modification were made.

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<sup>34</sup> '467 patent, at column 2, lines 18 to 26 (emphasis added).

In view of the foregoing, the Applicants respectfully request withdrawal of the obviousness rejection of claims 75, 77, 97, 99-103, 113-117, and 133.

**III. Conclusion**

In light of the foregoing, the Applicants request entry of the amendments to the claims, withdrawal of the claim rejections, and solicit an allowance of all pending claims.

The Commissioner is hereby authorized to change any and all fees that may be required or credit any overpayment to Deposit Account No. 50-1662.

Polsinelli Shalton Flanigan Suelthaus PC

Respectfully submitted,

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